Dramatic decline of serogroup C meningococcal disease incidence in Catalonia (Spain) 24 months after a mass vaccination programme of children and young people

L Salleras, A Domínguez, G Prats, I Parron, P Muñoz

Abstract

Study objectives—The objective of this study was to evaluate the effectiveness of a mass vaccination programme carried out in Catalonia (Spain) in the last quarter of 1997 in response to an upsurge of serogroup C meningococcal disease (SCMD).

Design—Vaccination coverage in the 18 month to 19 years age group was investigated by means of a specific vaccination register. Vaccination effectiveness was calculated using the prospective cohort method. Cases of SCMD were identified on the basis of compulsory reporting and microbiological notification by hospital laboratories. Vaccination histories were investigated in all cases. Unadjusted and age adjusted vaccination effectiveness referred to the time of vaccination and the corresponding 95% confidence intervals (CI) were estimated at 6, 12, 18 and 24 months of follow up.

Setting—All population aged 18 months to 19 years of Catalonia.

Main results—A total of seven cases of SCMD were detected at six months of follow up (one in the vaccinated cohort), 12 cases at 12 months (one in the vaccinated cohort), 19 cases at 18 months (two in the vaccinated cohort) and 24 at 24 months (two in the vaccinated cohort). The age adjusted effectiveness was 84% (95%CI 30, 97) at six months, 92% (95%CI 63, 98) at 12 months, 92% (95% CI 71, 98) at 18 months and 94% (95% CI 78, 98) at 24 months. In the target population, cases have been reduced by more than two thirds (68%) two years after the vaccination programme. In the total population the reduction was 43%.

Conclusion—Vaccination effectiveness has been high in Catalonia, with a dramatic reduction in disease incidence in the vaccinated cohort accompanied by a relevant reduction in the overall population. Given that vaccination coverage was only 54.6%, it may be supposed that this vaccination effectiveness is attributable, in part, to the herd immunity conferred by the vaccine.

Meningococcal disease is endemic in Spain, with hyperendemic episodes taking place every 10–15 years, which lead to higher incidence rates, such as in the 1979 upsurge that reached a level of 17 per 100 000 inhabitants.

In the past, serogroup B meningococcal disease was predominant, causing almost 80% of cases, with serogroups C and A next. However, this situation has changed. Serogroup A disappeared during the 1990s and from 1993 serogroup C meningococcal disease (SCMD) has increased, overtaking the declining number of serogroup B cases in 1996.

A marked rise in SCMD was registered from mid-1996 with serogroup C becoming the main serogroup in virtually all the regions of Spain. This was accompanied by the appearance of a new serogroup C strain—C:2b:P1.2,5—which in some communities led to higher case fatality rates.

Widespread media coverage of the upsurge caused considerable social alarm, which was heightened by the majority involvement of infants and adolescents.

The north western Spanish region of Galicia, where the upsurge first appeared, decided, in 1996, to respond with a campaign of mass vaccination of the 18 months to 19 years age group, a strategy that was taken up by La Rioja and Cantabria in early 1997. The other regions, except Andalusia, Navarra and the Canary Islands, decided to adopt this policy and carry out mass vaccination during the last three months of 1997.

The campaign took place in the last quarter of 1997 in Catalonia, with free vaccination taking place in primary health and paediatric centres. In the 18 months to 19 years age group, overall coverage was 54.6%, reaching 65.2% in the 18 months to 4 years group, 77.8% in the 5–9 years group, 60.8% in the 10–14 years group and only 31.4% among 15–19 year olds. The campaign was estimated to have cost around 4.5 million Euros.

Preliminary results after 6 and 12 months of follow up were presented at the 4th Europe—America Conference on Vaccinology.

In this article, mass vaccination effectiveness after 6, 12, 18 and 24 months of follow up is evaluated.

Methods

In Catalonia it is compulsory to report any suspected case of meningococcal disease to the health authorities. In all reported cases, cerebrospinal fluid and blood are cultivated to isolate the germ and identify the serogroup. In all confirmed cases of serogroup C, vaccination status is investigated.
Table 1  Distribution of confirmed cases of meningococcal disease in Catalonia, 1996–1999

<table>
<thead>
<tr>
<th>Year</th>
<th>Serogroup B</th>
<th>Serogroup C</th>
<th>Serogroup A</th>
<th>Serogroup W</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>123</td>
<td>64</td>
<td>2</td>
<td>49</td>
<td>2</td>
<td>194</td>
</tr>
<tr>
<td>1997</td>
<td>102</td>
<td>28</td>
<td>0</td>
<td>13</td>
<td>1</td>
<td>148</td>
</tr>
<tr>
<td>1998</td>
<td>77</td>
<td>28</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>113</td>
</tr>
<tr>
<td>1999</td>
<td>113</td>
<td>33</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>151</td>
</tr>
</tbody>
</table>

Table 2  Distribution of cases of serogroup C meningococcal disease according to the period of follow up and the vaccination status

<table>
<thead>
<tr>
<th>Age at the time of vaccination</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccinated</td>
<td>Unvaccinated</td>
<td>Vaccinated</td>
<td>Unvaccinated</td>
</tr>
<tr>
<td>18 months–4 years</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5–9 years</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10–13 years</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>15–19 years</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

Results

Table 1 shows the distribution of all confirmed cases of meningococcal disease according to the serogroup during the period 1996–1999. A substantial reduction in the incidence of SCMD occurred during the follow up period. In total, during 1998, 28 cases of SCMD were reported, in comparison with the 77 reported during the preceding year. In the target vaccination age group, cases were reduced after 24 months of follow up by more than two thirds (16 cases in 1999 compared with 50 in 1997). The cases in this age group occurred almost exclusively in unvaccinated subjects (22 cases) with only two cases occurring in vaccinated children. It should be noticed that the incidence of unvaccinated cases was higher in older children, the age group with lower vaccination coverage. In the total population the reduction was also relevant (43%).

The target population according to the 1996 census returns was 1 273 348 and the global vaccination estimated vaccination coverage was 54.6, although this figure changed over age groups (see table 2). Thus, the vaccinated cohort was 694 814 subjects and the unvaccinated one 578 534. So, for the follow up period of 24 months, the number of persons year for each cohort was 1 389 628 and 1 157 068 respectively. The number of SCMD during the 24 months follow up period was 24 (two in the vaccinated cohort and 22 in the unvaccinated cohort). Thus, the incidence rate in the vaccinated cohort was 0.14 per 100 000 persons per year and in the unvaccinated one 5.26 per 100 000 persons per year. The unadjusted vaccination effectiveness was 92%; 95% CI, 68 to 98%.

For the calculation of the lower and upper limits of the relative risk (RR), Estimates of relative risk (RR) and 95% CI were calculated with and without stratification for the age at the time of vaccination.

To obtain lower and upper limits of VE the following formulas were used:

- Lower limit of VE = (1−RR l ) × 100, where RR l is the lower limit of RR.
- Upper limit of VE = (1−RR u ) × 100, where RR u is the upper limit of RR.

The reduction of the number of cases was highly significant (p<0.001). The adjusted vaccination effectiveness was 92%; 95% CI, 68 to 98%.

These calculations by periods of follow up (6, 12, 18 and 24 months) are shown in table 3. No relevant differences have been observed in vaccination effectiveness according to the duration of follow up. Adjusted vaccination effectiveness shows similar results with narrower confidence limits.
Table 4  Efficacy and effectiveness* of meningococcal C vaccine in published studies

<table>
<thead>
<tr>
<th>Country (year)</th>
<th>Author</th>
<th>Type of study</th>
<th>Number</th>
<th>Age</th>
<th>Design</th>
<th>Follow up period</th>
<th>Efficacy/ Effectiveness %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (1969)</td>
<td>Artenstein et al.</td>
<td>Efficacy</td>
<td>68 000</td>
<td>6 months</td>
<td>Randomised controlled trial</td>
<td>2 months</td>
<td>87†</td>
<td>75, 100†</td>
</tr>
<tr>
<td>USA (1969/70)</td>
<td>Gold et al.</td>
<td>Efficacy</td>
<td>75 000</td>
<td>6 months</td>
<td>Randomised controlled trial</td>
<td>2 months</td>
<td>88†</td>
<td>52, 100†</td>
</tr>
<tr>
<td>Brazil (1972)</td>
<td>Taunay et al.</td>
<td>Efficacy</td>
<td>135 000</td>
<td>6 months</td>
<td>Randomised controlled trial</td>
<td>17 months</td>
<td>NS</td>
<td>(87)†</td>
</tr>
<tr>
<td>Italy (1987/89)</td>
<td>Biselli et al.</td>
<td>Efficacy</td>
<td>300 000</td>
<td>6 months</td>
<td>Incident</td>
<td>12 months</td>
<td>91†</td>
<td>30, 99†</td>
</tr>
<tr>
<td>Quebec (1992/93)</td>
<td>De Wallis et al.</td>
<td>Efficacy</td>
<td>1.7 million</td>
<td>6 months–20 years</td>
<td>Incident</td>
<td>4 years</td>
<td>79</td>
<td>53, 91</td>
</tr>
<tr>
<td>Gregg County (1993/95)</td>
<td></td>
<td>Efficacy</td>
<td>17 cases</td>
<td>6 months–4 years</td>
<td>Case-control</td>
<td>(72)</td>
<td>(5, 91)</td>
<td></td>
</tr>
<tr>
<td>Catalonia (Spa) (1998–99)</td>
<td>Rosenstei</td>
<td>Efficacy</td>
<td>84 controls</td>
<td>2–29 years</td>
<td>Incident</td>
<td>12 months</td>
<td>92</td>
<td>63, 98</td>
</tr>
<tr>
<td></td>
<td>n et al.†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18 months</td>
<td>92</td>
<td>71, 98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24 months</td>
<td>94</td>
<td>78, 98</td>
</tr>
</tbody>
</table>

*Data in parentheses refer to specific population subgroups. †Recalculated by Rosenstein et al.14
The conjugation with proteins of the capsular polysaccharide converts it into T dependent antigen and makes the vaccine immunogenic in breast feeding babies and also generates antigen and makes the vaccine immunogenic in lar polysaccharide meningococcal vaccines conjugated with proteins. These vaccines have been tested in Africa and the UK, with promising results.

The excellent results obtained in Catalonia in controlling the SCMD upsurge by mass vaccination supports both the recently taken decision of the UK Medicines Control Agency to license production of the new conjugated meningococcal C polysaccharide vaccine without implementing field trials of efficacy and the English Government's decision to begin mass vaccination of children and young people.30

The authors are grateful to Professor M J Campbell and Dr E Cobo for their comments and suggestions and to all the reporting physicians, the staff of the epidemiological surveillance units and the microbiological laboratories that have participated in the notification of the cases and in the collecting of vaccination antecedents.

Funding: none.

Conflicts of interest: none.

Appendix

As suggested by Kleinbaum et al and Ewell,11 Y, y, Y, denote the number of person years of follow up in vaccinated and non-vaccinated respectively in whom C, c, y C, cases of infection have been observed in the corresponding groups. It is supposed that the incidence in the respective groups are independent. In this case, the relative risk (RR) is calculated by:

\[ RR = \frac{c_1/Y_1}{c_0/Y_0} \]  

(1)

Firstly, the natural log transformation of the relative risk is calculated, as we assume the asymptotic normality of this transformation.

The variance of this new variable (ln RR) is obtained

\[ \text{var(ln RR)} = \text{var} \left( \ln \left( \frac{c_1/Y_1}{c_0/Y_0} \right) \right) \]

\[ = \text{var} \left( \ln(c_1/Y_1) - \ln(c_0/Y_0) \right) \]

\[ = \text{var} \left( \ln(c_1/Y_1) \right) + \text{var} \left( \ln(c_0/Y_0) \right) \]  

(2a)

and approximating \( \text{var} (\ln(c_i/Y_i)) \), \( i = 0, 1 \), by Taylor's series we obtain

\[ \text{var} (\ln(c_i/Y_i)) \sim \left( \frac{1}{c_i/Y_i} \right)^2 \text{var}(c_i/Y_i) \]  

(3a)

Substituting (3a) for (2a), we obtain

\[ \text{var}(\ln RR) \sim \frac{1}{c_1} - \frac{1}{c_0} \]  

\[ + \frac{1}{c_1} - \frac{1}{c_0} \]

(4a)

According to the hypothesis of asymptotic normality of the transformation mentioned above, the confidence intervals calculated at (1-\( \alpha \))-% for the variable ln RR are obtained by the following equation

\[ \ln RR \pm Z_{1-\alpha/2} \sqrt{\text{var}(\ln RR)} \]  

(5a)

and thus, the lower and upper limits of the relative risk, named RR, y RR, respectively are obtained by the equation

\[ RR \times \exp \left( \pm Z_{1-\alpha/2} \sqrt{\text{var}(\ln RR)} \right) \]

\[ = RR \times \exp \left( \pm Z_{1-\alpha/2} \sqrt{\left( \frac{1}{c_1} - \frac{1}{c_0} \right)} \right) \]  

(6a)

Finally, the confidence intervals of vaccine effectiveness are calculated in function of the intervals obtained for the relative risk using the expression (6a):

\[ (VE_L, VE_U) = (1-RR_U, 1-RR_L) \]
Serogroup C meningococcal disease incidence